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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/823,784

04/14/2004

Karen Uhlmann

3035-101

4952

46002 7590 05/15/2008

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EXAMINER

SHAW, AMANDA MARIE

ART UNIT

PAPER NUMBER

1634

MAIL DATE

DELIVERY MODE

05/15/2008

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	Application No. 10/823,784	Applicant(s) UHLMANN ET AL.	
	Examiner AMANDA SHAW	Art Unit 1634	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 28 April 2008 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

- a) ☐ The period for reply expires _____ months from the mailing date of the final rejection.
- b) ☒ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
- (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
- (b) ☐ They raise the issue of new matter (see NOTE below);
- (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
- (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☒ Applicant's reply has overcome the following rejection(s): See Continuation Sheet.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
- The status of the claim(s) is (or will be) as follows:
- Claim(s) allowed: none.
- Claim(s) objected to: none.
- Claim(s) rejected: 1-5,7-20 and 22-39.
- Claim(s) withdrawn from consideration: none.

AFFIDAVIT OR OTHER EVIDENCE

8. ☒ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing of good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

/Juliet C Switzer/
Primary Examiner, Art Unit 1634

Continuation of 5. Applicant's reply has overcome the following rejection(s): The rejection made under 35 USC 112 2nd paragraph in section 4 of the Office Action of February 28, 2008 is withdrawn in view of amendments made to the claims.

Continuation of 11. does NOT place the application in condition for allowance because: Regarding the rejection made under 35 USC 103(a) over Uhlmann in view of Nyren the Applicants argue that a person skilled in the art would be reluctant to make the modification to Uhlmann that the Office suggested, namely detectably labeled Uhlmann's amplification primers because it would interfere with Uhlmann's subsequent cloning step. Further the Applicants argue that the modification proposed by the Office would render Uhlmann unsatisfactory for its intended purpose. The Applicants refer to MPEP 2143.01 and *In re Gordon* 733 F. 2d 900, 221 USPQ 1125 (Fed. Cir. 1984) for support. This argument has been fully considered but is not persuasive. First of all the intended purpose of Uhlmann is not cloning, it is sequencing in order to determine if methylation is present. The substitution of the sequencing method of Uhlmann (which requires a cloning step) for the sequencing step of Nyren (which does not require a cloning step) would not render Uhlmann unsatisfactory for its intended purpose because the intended purpose is to determine the sequence of the nucleic acid, which Nyren clearly does. Again it is noted that the claims do not require a cloning step. Therefore labeling the primers as suggested by Nyren would not interfere with the sequencing method of Nyren.

Next the Applicants point to a recent discussion of non-obviousness in *Ortho-McNeil Pharmaceutical v. Mylan Labs*, 2008-1223, Fed Cir. March 31, 2008. This case deals with hindsight analysis. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Additionally the Applicants argue that the Examiner did not consider all of the Applicants arguments of non-obviousness. First the Applicants point to an email between John Dixon and Karl Voss regarding technical difficulties associated with using biotinylated primers. This email was previously considered but it is not clear how this is relevant to the instant claims especially since the biotinylated primers do not interfere with the sequencing method of Nyren. For example its unclear why it matters if the presence of biotin on a PCR primer lowers the annealing temperature of the primer. Further just because John Dixon could not get one biotinylated primer to work does not mean that all biotinylated primers will not work. It is further noted that the email exchange is not considered to be proper evidence. Also the Applicants claim that they point out that other technical difficulties would have been expected from combining Uhlmann and Nyren. Specifically they state that the pyrosequencing mixture is more complex than the dideoxynucleotide chain termination sequencing mixture and that the effects of a chemical modification of the DNA and any residual chemicals were unclear at the time the invention was made. This argument has previously been considered but is not persuasive because the Applicants are attempting to provide a showing of unexpected results however they have not provided any evidence to support this.

The Applicants also argue that the Examiner did not consider all of the limitations of claim 12. They argue that step (d) requires detecting whether said nucleotide is methylated or not methylated at said predetermined position in the sample to diagnose said pathological condition or the predisposition for said pathological condition. This was addressed in the previous Office action and is considered to be an intended use. The claims do not have an actual method step of "diagnosing". The only actual step required in (d) is "detecting whether said nucleotide is methylated or not methylated". Thus the combined references teach all of the active process steps required by the claims. Further even if the claims were amended to actually require a "diagnosing" step they would still be rejected because Uhlmann teaches an association between hypomethylation and pilocytic astrocytomas and Nyren teaches pyrosequencing can be used to detect disease.

Finally with regard to claim 39 the Applicants submit that by the reference to "is detected" claim 39 does require a detection of an allele frequency of 5%. This argument has been fully considered but is not persuasive because claim 39 depends from claim 34 which says "can be detected" which does not necessarily mean that it is detected.

For these reasons all of the art rejections are maintained.

Further it is noted that any arguments addressing the Declaration that has been submitted are considered moot in view of the non entry of the Declaration.